PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 May 2000 (11.05.00)	
International application No. PCT/US99/19725	**Applicant's or agent's file reference** 1331-297
International filing date (day/month/year) 31 August 1999 (31.08.99)	**Priority date** (day/month/year) 31 August 1998 (31.08.98)
Applicant VON BORSTEL, Reid, W.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 March 2000 (30.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: THOMAS E. BYRNE
NIXON & VANDERHYE, P.C.
1100 NORTH GLEBE R[redacted]
SUITE 800
ARLINGTON, VA 22201-4714

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	09 JAN 2001
Applicant's or agent's file reference: 1331-297	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/19725	31 AUGUST 1999	31 AUGUST 1998

Applicant: PRO-NEURON, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	RICHARD SCHNIZER DELLA MAE COLLINS PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992)★

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1331-297	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/19725	International filing date *(day/month/year)* 31 AUGUST 1999	Priority date *(day/month/year)* 31 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A01N 43/04; A61K 31/70 and US Cl.: 514/49		
Applicant PRO-NEURON, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand 30 MARCH 2000	Date of completion of this report 17 NOVEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD SCHNIZER Telephone No. (703) 308-0196

DELLA MAE COLLINS
PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600

Form PCT/IPEA/409 (cover sheet) (July 1998)★

I. Basis f the report

1. With regard to the elements o international application:*

[X] the international application as originally filed

[X] the description:
pages 1-49 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 50-54 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	2-10, 15, 16, 18, 21-45, 47	YES
	Claims	1, 11-14, 17, 19, 20, 46	NO
Inventive Step (IS)	Claims	15, 16, 45	YES
	Claims	1-14, 17-44, 46, 47	NO
Industrial Applicability (IA)	Claims	1-47	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1, 11-14, 19, and 20 lack novelty under PCT Article 33(2) as being anticipated by Von Borstel et al (US Patent 5,470,838).

Von Borstel teaches treatment of Parkinson's disease with acylated uridine and cytidine derivatives, particularly 2', 3', 5'-tri-O-acetylcytidine and 2', 3', 5'-tri-O-acetyluridine (col. 13, lines 54-56; and col. 15 lines 6-12). The instant specification defines Parkinson's disease as being characterized by mitochondrial respiratory chain dysfunction (see claim 24). Therefore, claims 1 and 11-14 are anticipated by US Patent 5,470,838 because the effects of 2', 3', 5'-tri-O-acetylcytidine and 2', 3', 5'-tri-O-acetyluridine are inherent in their structures. 2', 3', 5'-tri-O-acetyluridine may be administered in doses up to 4.5 g/day.

Claims 1, 11, and 17 lack novelty under PCT Article 33(2) as being anticipated by Secades et al (Methods and Findings in Experimental and Clinical Pharmacology, 1995).

Secades teaches the treatment of Alzheimer's and Parkinson's diseases with cytidine diphosphocholine (CDP-choline) (see page 38, col. 2 through page 39 col. 1)

Claim 46 lacks novelty under PCT Article 33(2) as being anticipated by Keilbaugh et al (Database MEDLINE, Accession No. 940496698).

Keilbaugh teaches the administration of uridine and pyruvate to PC12 cells, and suggests this as a treatment for peripheral neuropathy in patients undergoing 2',3'-dideoxycytidine therapy (see entire abstract).

Claims 1, 11, 18, 19, and 23-25 lack an inventive step under PCT Article 33(3) as being obvious over Secades in view of Dykens (J. Neurochem., 1994).

The invention is a method for treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction with a pyrimidine nucleotide precursor. The precursor may be cytidine, it may be administered in a dose of (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
0.01-1 gram per kilogram bodyweight per day, and it may be administered orally. The pathology to be treated may be a neurodegenerative disease, particularly Alzheimer's or Parkinson's. A further embodiment of the invention is a method of diagnosing mitochondrial disease by administration of a pyrimidine nucleotide precursor followed by clinical assessment of disease progress. Another embodiment of the invention is a pharmaceutical composition comprising a pyrimidine nucleotide precursor.

As stated in the previous objection, Secades teaches the treatment of Alzheimer's and Parkinson's diseases with CDP-choline. More specifically, Secades teaches that patients with either early- or late-onset Alzheimer's were given 1 g/day of CDP-choline orally, and these patients responded with improved cognitive function (see page 38, col. 2 through page 39 col. 1). Secades provides several examples of the intravenous or intramuscular administration of CDP-choline for the treatment of Parkinson's disease (see pages 40-43). In one example, patients were administered 600 mg/day intravenously and subsequently displayed improved symptoms (bradykinesia, rigidity and trembling were assessed, also see page 41, col. 1, and Table 18 for description of a study by Acosta et al). Secades also teaches that after oral administration ,CDP-choline breaks down to release cytidine and choline which are completely absorbed (see second sentence of abstract; and page 21, col. 2, to page 22; and Figs. 11 -13). Thus, administration of CDP-choline is pharmacologically similar to administration of choline and the pyrimidine nucleotide precursor cytidine, separately. Secades does not explicitly teach that respiratory dysfunction is observed in Parkinson's disease patients, Huntington's disease patients, or Alzheimer's disease patients.

Dykens teaches that respiratory chain dysfunction is observed in mitochondria isolated from Parkinson's disease patients, Huntington's disease patients, and Alzheimer's disease patients (see lines 24-28 of abstract; and page 589, col. 1, first para.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat either Parkinson's or Alzheimer's diseases with cytidine and choline. One would have been motivated to do so because Secades describes treatment of these disorders with CDP-choline, wherein the treatments alleviate certain symptoms of the diseases, and because Dykens teaches that these disorders are characterized by respiratory chain dysfunction. It would have been similarly obvious to treat these diseases with either cytidine or choline. One of ordinary skill in the art would have been motivated to do so to discern their relative contributions to the relief of symptoms.

Claims 2-10, 21, 22, 26-43, and 47 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Bodnar (Biochem. J., 1995).

The invention comprises methods of treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction by administration of a pyrimidine nucleotide precursor. In a further embodiment of the invention, pyruvic acid, an acceptable salt of pyruvate, or a pyruvic acid ester may be used in combination with the pyrimidine nucleotide precursor. The respiratory dysfunction can be due to a variety of causes, particularly loss of function mutations in genes whose products are required for respiration. The pathophysiological consequence can be any of a wide variety of disorders affecting a wide variety of tissues. In each method, the primary effect of treatment is the relief of respiratory chain dysfunction. For this reason, nonobviousness is attributed only to the mode of treatment of respiratory chain dysfunction, and not to any of the causes or effects of respiratory chain dysfunction.

The teachings of Secades and Dykens are summarized in the previous two objections. Briefly, Secades teaches the rapid degradation of CDP-choline to cytidine and choline upon administration, and the treatment of Alzheimer's and Parkinson's diseases by administration of CDP-choline. Secades further teaches that treatment with CDP-choline positively affects mitochondrial respiration by restoring and protecting mitochondrial ATPase activity in cases of traumatic cerebral injury (page 4, last full paragraph, through page 5, col. 1. See abstract as well). Secades does not explicitly teach that respiratory dysfunction is associated with any of the diseases recited in the claims. Secades does not teach the use of pyruvate in the treatment of respiratory dysfunction.

Dykens teaches that respiratory chain dysfunction is observed in mitochondria isolated from Parkinson's disease patients, Huntington's disease patients, and Alzheimer's disease patients (see lines 24-28 of abstract; and page 589, col. 1, first para. Dykens does not teach treatment of patients with pyruvate or pyrimidine nucleotide precursors.

Bodnar teaches that fibroblasts isolated from patients with mitochondrial respiratory dysfunction require both pyruvate and uridine supplementation for growth after several generations in culture (see abstract, lines 6-10).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat respiratory chain disorders by administration of the pyrimidine nucleotide precursor cytidine. One of skill in the art would have noted that CDP-choline had a positive effect on mitochondrial respiration as shown by Secades. Further, one would have noted the correlation of respiratory dysfunction in Parkinson's and Alzheimer's diseases with the positive effect of CDP-choline on these disorders. The observation of these data would have provided motivation to attempt treatment of respiratory dysfunction in general with cytidine and choline. In particular one would have been motivated to treat Huntington's disease because Dykens teaches the correlation of respiratory dysfunction with this disease. As stated in the previous objection, one would have been further motivated to use cytidine and choline separately in order to determine their relative contributions to the treatment.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to attempt to treat

Supplemental B x
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

mitochondrial respiratory dysfunction with pyruvate and uridine, because Bodnar demonstrates that these supplements restore normal cellular growth rates to cells which lack proper respiratory function. One of ordinary skill in the art is aware of the correlation between respiratory function and growth rate, and would therefore be motivated to use uridine in combination with pyruvate to treat diseases associated with respiratory dysfunction.

Claim 44 lacks an inventive step under PCT Article 33(3) as being obvious over Keilbaugh et al (Database MEDLINE, Accession No. 940496698).

The invention is a method of diagnosing mitochondrial disease in a mammal by administering a pyrimidine nucleotide precursor and assessing subsequent clinical improvement.

Keilbaugh teaches the administration of uridine and pyruvate to PC12 cells, and suggests this as a treatment for peripheral neuropathy in patients undergoing 2',3'-dideoxycytidine therapy (see entire abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer drugs to a patient, observe the subsequent clinical progress of the patient, and draw conclusions about the patient's disease based upon the observations. One of ordinary skill in the art appreciates that this is standard medical procedure, and would therefore be motivated to perform this method.

---------- NEW CITATIONS ----------
NONE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19725

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : A01N 43/04; A61K 31/70
US CL : 514/49
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/49

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: medline, caplus, biosis, embase, biotechds

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X – A	US 5,470,838 A (VAN BORSTEL) 28 November 1995, col. 13, lines 54-56; and col. 15, lines 6-12.	1, 11-14 ——— 15,16,44
X – Y – A	SECADES et al. CDP-Choline: Pharmacoligical and Clinical Review. Methods and Findings in Experimental and Clinical Pharmacology. October 1995, Vol. 17, Supplement 1, pages 1-54, especially abstract, page 4, last full paragraph through page 5 col. 1; page 21, col.2 through page 22, and Figs, 11-13; page 38, col. 2 through page 39 col. 1; pages 40-43, especially page 41, col.1, and Table 18.	1, 11, 17 ——— 1-11,18-42, 46 ——— 15,16,44

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 OCTOBER 1999	Date of mailing of the international search report 03 NOV 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD SCHNIZER Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19725

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	Database Medline on STN AN 94049698, KEILBAUGH et al. Anti-human immunodeficiency virus type 1 therapy and peripheral neuropathy: prevention of 2', 3'-dideoxycytidine toxicity in PC 12 cells, a neuronal model, by uridine and pyruvate. Molecular Pharmacology. October 1993. Vol. 44. No. 4. pages 702-706, abstract only.	45 ---- 43
Y	DYKENS, J.A. Isolated cerebral and cerebellar mitochondria produce free radicals when exposed to elevated Ca2+ and Na+: Implications for neurodegeneration. Journal of Neurochemistry. 1994, Vol. 63, pages 584-591, especially lines 24-28 of abstract; and page 589, col. 1. first paragraph.	1-11,18-42, 46
Y	BODNAR et al. Respiratory-deficient human fibroblasts exhibiting defective mitochondrial DNA replication. Biochem. J. 1995, Vol. 305, pages 817-822, especially abstract lines 6-10.	2-10, 20, 21, 25-42, 46